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## Working Safely with Radioactive Materials

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The information within this chapter is designed as a supplement, not a replacement, to the training provided by your institutional rules and/or radiation safety officer. At the very least, there are some 10 fundamental rules to consider when working with radioactivity (Amerhsam International, 1974):

1. Understand the nature of the hazard, and get practical training.
2. Plan ahead to minimize time spent handling radioactivity.

3. Distance yourself appropriately from sources of radiation.
4. Use appropriate shielding for the radiation.
5. Contain radioactive materials in defined work areas.
6. Wear appropriate protective clothing and dosimeters.
7. Monitor the work area frequently for contamination control.
8. Follow the local rules and safe ways of working.
9. Minimize accumulation of waste and dispose of it by appropriate routes.
10. After completion of work, monitor yourself; then wash and monitor again.

## **LICENSING AND CERTIFICATION**

### **Do You Need a License to Handle Radioactive Materials?**

Whichever type of license is granted by the Nuclear Regulatory Commission (NRC), it tends to be a single license issued to the institution itself, to regulate its entire radioisotope usage. Separate licenses are not normally granted to the various departments or to individuals at that institution. However, everyone who works with radioactive materials at a licensed institution must be trained and approved to use the radioactive materials. Keep in mind that some states may have control over radioactive materials not controlled by the NRC. In addition, in “agreement states,” the NRC requirements are regulated and controlled by a state agency.

Universities, governmental institutions, or industry are usually licensed to use radionuclides under a Type A License of Broad Scope (U.S. Nuclear Regulatory Commission Regulatory Guide, 1980). This is the most comprehensive license available to an institution. It requires that the institution have a radiation safety committee, an appointed radiation safety officer (RSO), and detailed radiation protection and training procedures. Researchers who want to use radionuclides in their work must present the proposal to the radiation safety committee and have it approved before being able to carry out the experiments.

There are other types of licenses issued by NRC or by agreement states. For example, these may be specific by-product material licenses of limited scope, specific licenses of broad scope, licenses for source or special nuclear materials, or licenses for kilocurie irradiation sources (U.S. Nuclear Regulatory Commission Regulatory Guide, 1979, 1976). By-product materials are the radionuclides that form during reactor processes. The most commonly used radionuclides,  $^{32}\text{P}$ ,  $^{33}\text{P}$ ,  $^{35}\text{S}$ ,  $^3\text{H}$ ,  $^{14}\text{C}$ , and  $^{125}\text{I}$  are all by-product materials. The licensing of by-product material is

covered in detail under Title 10, Code of Federal Regulations (CFR), Part 30, *Rules of General Applicability to Licensing of Byproduct Material* (10CFR Part 30), and 10CFR Part 33, *Specific Domestic Licenses of Broad Scope for Byproduct Material* (10CFR Part 33).

For more information, a recent publication by the NRC is now available entitled: *Consolidated Guidance about Materials Licenses. Program-Specific Guidance about Academic Research and Development, and other Licenses of Limited Scope*. Final Report U.S. Regulatory Commission, Office of Nuclear Material Safety and Safeguards. NUREG-1556, Vol. 7. M. L. Fuller, R. P. Hayes, A. S. Lodhi, G. W. Purdy, December 1999. You can also find information on the NRC Web site [www.NRC.gov](http://www.NRC.gov). The Atomic Energy Control Board, or AECB, governs radioactive use in Canada. Their Web site is [www.aecb-ccea.gc.ca](http://www.aecb-ccea.gc.ca).

### **Who Do You Contact to Begin the Process of Becoming Licensed or Certified to Use Radioactivity?**

If you want to use radioactivity in your research, you may need to become an authorized user at your institution. First, decide what type of isotope or isotopes will be used in your research, the application, how much material you will need, disposal methods, and for how long you will use it. Then, present this information to your radiation safety officer or radiation safety committee so that they can determine whether such radionuclide use is possible under your institution's license. If the request is approved, carry out the requirements stated on your institution's license to become an authorized user operating in an approved laboratory.

## **SELECTING AND ORDERING A RADIOISOTOPE**

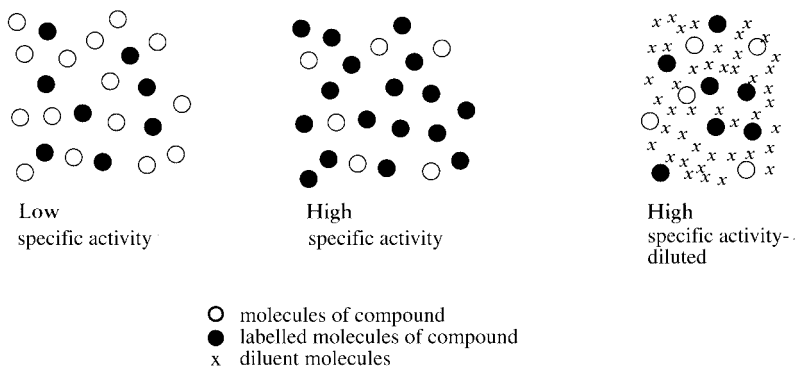
### **Which Radiochemical Is Most Appropriate for Your Research?**

#### *The Institution's Perspective*

Your institution's license defines specific limits to the type and amount of radionuclide allowable on site (this includes on-site waste). Before determining how much material you think you'll need, find out how much you'll be allowed to have in your lab at any one time. You can then get an idea about how or if you'll need to space out the work requiring radioactivity.

#### *Your Perspective*

These are some of the most important parameters to consider when deciding which isotope to use.



**Figure 6.1** Diagrammatical representation of radiochemicals at low and high specific activity, and at high specific activity in a diluent. From *Guide to the Self-decomposition of Radiochemicals*, Amersham International, plc, 1992, Buckinghamshire, U.K. Reprinted by permission of Amersham Pharmacia Biotech.

### Radionuclide, Energy, and Type of Emission (Alpha, Beta, Gamma, X ray, etc.)

In most cases you won't have the choice. You will choose the radionuclide because of its elemental properties, and its reactivity in reference to the experiment, not its type of emission. Each radionuclide has its unique emission spectrum. The spectra are important in determining how you detect the radioactivity in your samples. This is discussed more fully later in the chapter.

### Specific Activity and Radioactive Concentration

The highest specific activity and the highest radioactive concentration tend to be the best since it means that there will be the greatest number of radioactive molecules in a given mass and volume (Figure 6.1). But there are two caveats to this ideal. The first is that as you increase the specific activity, you decrease the molar concentration of your desired molecule. This molecule will become the limiting reagent and possibly slow down or halt the reaction. The second danger is that at high specific activities and/or radioactive concentrations, the rate of radiolytic decomposition will increase. These parameters are discussed in more detail in Chapter 14, "Nucleic Acid Hybridization."

To take an example, a standard random priming labeling reaction requires 50  $\mu\text{Ci}$  (1.85 MBq)\* of  $^{32}\text{P}$  dNTP (Feinberg

*\*In the United States the unit of activity of "Curie" is still used. The unit of common usage is the Becquerel (Bq). Whereas 1 Curie =  $3.7 \times 10^{10}$  disintegrations per second (dps), the Bq = 1 dps. For example, to convert picocuries ( $10^{-12}$  Curies) to*

and Vogelstein, 1983). At a specific activity of 3000 Ci/mmol, that 50  $\mu$ Ci translates to 16.6 femtomoles of  $^{32}\text{P}$  dNTP being added to the reaction mix, while 50  $\mu$ Ci of a  $^{32}\text{P}$  labeled dNTP at a specific activity of 6000 Ci/mmol will add only 8.3 femtomoles to the reaction. Unless sufficient unlabeled dNTP is added, the lower mass of the hotter dNTP solution added might end up slowing the random prime reaction down, giving the resulting probe a lower specific activity than the probe that used the 3000 Ci/mmol material.

#### Label Location on the Compound

Consider the reason for using a radioactive molecule. Is the reaction involved in the transferring of the radioactive moiety to a biomolecule, such as a nucleic acid, peptide, or protein? Is the *in vivo* catabolism of the molecule being studied, perhaps in an ADME (absorption, distribution, metabolism, and excretion) study? Or perhaps the labeled molecule is simply being used as a tracer. For any situation, it's worthwhile to consider the following impacts of the label location: First, will the label's location allow the label or the labeled ligand to be incorporated? Next, once incorporated, will it produce the desired result or an unwanted effect? For example, will the label's presence in a nucleic acid probe interfere with the probe's ability to hybridize to its target DNA? The latter issue is also discussed in greater detail in Chapter 14, "Nucleic Acid Hybridization."

There are some reactions where the location of label is not critical. A thymidine uptake assay is one such case. The labeling will work just as effectively whether the tritium is on the methyl group or on the ring.

#### The Form and Quantity of the Radioligand

The radionuclide is usually available in different solvents. The two main concerns are the effect (if any) of the solvent on the reaction or assay, and whether the radioactive material will be used quickly or over a long period. For example, a radiolabeled compound supplied in benzene or toluene cannot be added directly to cells or to an enzyme reaction without destroying the biological systems; it must be dried down and brought up in a compatible solvent. Likewise a compound shipped in simple aqueous solvent might be added directly to the reaction, but might not be

*Becquerels, divide by 27 (27.027):*  $50 \mu\text{Ci} = 50 \times 10^{-6} \text{Ci} = (50 \times 10^{-6} \text{Ci} \times 3.7 \times 10^{10} \text{dps/Ci}) = 1.85 \times 10^6 \text{dps} = 1.85 \times 10^6 \text{Bq} = 1.85 \text{MBq.}$

the best solvent for long-term storage. From a manufacturing perspective, the radiochemical is supplied in a solvent that is a compromise between the stability and solubility of the compound and the investigator's convenience.

Some common solvents to consider, and the reasons they are used:

- *Ethanol, 2%*. Added to aqueous solvents where it acts as a free radical scavenger and will extend the shelf life of the radiolabeled compound.
- *Toluene or benzene*. Most often used to increase stability of the radiolabeled compound, and increase solubility of nonpolar compounds, such as lipids.
- *2-mercaptoethanol, 5 mM*. Helps to minimize the release of radioactive sulfur from amino acids and nucleotides in the form of sulfoxides and other volatile molecules.
- *Colored dyes*. Added for the investigator's convenience to visualize the presence of the radioactivity.

When not in use, the “stock” solution of the radioactive compound is capped and usually refrigerated to minimize volatilization/evaporation.

### **What Quantity of Radioactivity Should You Purchase?**

There are three things to consider when deciding how much material to purchase:

1. How much activity (radioactivity) will be used and over what period?
2. What are the institutional limits affecting the amounts of radioisotope chosen that your lab may be authorized to use?
3. What are the decomposition rate of your radiolabeled compound and its half-life.

In general you will want to purchase as large a quantity as possible to save on initial cost, while at the same time not compromising the quality of the results of the research by using decomposed material. For example, certain forms of tritiated thymidine can have radiolytic decomposition rates (thymidine degradation) of 4% per week. This decomposition rate is not to be confused with tritium's decay rate, or half-life, which is over 12 years. Stocking up on such rapidly decomposing material, or by using it for more than just a few months could compromise experiments carried out later in the product's life.



## When Should You Order the Material?

### *Analysis Date*

Ideally you will want to schedule your experiments and your radiochemical shipments such that the material arrives at its maximum level of activity and lowest level of decomposition. This will tend to be when the product is newer, or nearer its analysis date (the date on which the compound passes quality control tests and is diluted appropriately so that the radioactive concentration and specific activity will be as those stated on the reference date). Some isotopes and radiochemicals decompose slowly, so it is not always necessary to take this suggestion to the extreme. As you use a radiolabeled product, you'll come to know how long you can use it in your work. An  $^{125}\text{I}$  labeled ligand will not last as long as a  $^{14}\text{C}$  labeled sugar. An inorganic radiolabeled compound, such as  $\text{Na}^{125}\text{I}$  or sodium  $^{51}\text{Cr}$  chromate, will decompose at the isotope's rate of decay, whereas a labeled organic compound, such as the tritiated thymidine alluded to earlier, will decompose at a much faster rate than the half-life of the isotope would indicate. Manufacturers take this into account by having a terminal sale date. The material will only be sold for so long before it is removed from its stores. Up until this date you will be able to purchase the material and still expect to use it over a reasonable period of time.

### *Reference Date*

The reference date is the day on which you will have the stated amount of material. If you purchased a 1 mCi vial of  $^{32}\text{P}$  dCTP, you will have greater than 1 mCi (37 MBq) prior to the reference date, 1 mCi on that date, and successively less beyond the reference date. (Note that since you will most likely receive your radioactive material prior to reference, it is possible to exceed possession limits; consider this when determining limits on your radiation license.) In the case of longer-lived radioisotopes, such as  $^3\text{H}$  and  $^{14}\text{C}$ , the analysis date will also serve as the reference date.

## How Do You Calculate the Amount of Remaining Radiolabel?

The most straightforward way of calculating radioactive decay is to use the following exponential decay equation. For convenience's sake, most manufacturers of radiochemicals provide decay charts in their catalogs for commonly used isotopes. This equation comes in handy for the less common isotopes.

$$A = A_0 e^{-0.693t/T}$$

where

$A_0$  is the radioactivity at reference date,

$t$  is the time between reference date and the time you are calculating for,

$T$  is the half-life of the isotope (note that both  $t$  and  $T$  must have the same units of time).

It is easy to use the aforementioned decay charts as shown in the following two examples.

Say you had 250  $\mu\text{Ci}$  of  $^{35}\text{S}$  methionine at a certain reference date, and the radioactive concentration was 15 mCi/ml. Now it is 25 days after that reference date. You calculate your new radioactive concentration and total activity in the vial by looking on the chart to locate the fraction under the column and row that corresponds to 25 days postreference. This number should be 0.820. Multiply your starting radioactive concentration by this fraction to obtain the new radioactive concentration:

$$15 \text{ mCi/ml} \times 0.820 = 12.3 \text{ mCi/ml}$$

The total amount of activity can be likewise calculated for  $^{35}\text{S}$  with a half-life of 87.4 days; namely  $A = A_0 e^{-0.693t/T} = 15 \exp(-0.693 \times 25/87.4) = 12.3 \text{ mCi/ml}$ .

For the second example you can find out how much activity you had before the reference date. Some decay charts only have postreference fractions, but if you have a 1 mCi vial of  $^{33}\text{P}$  dUTP at 10 mCi/ml, and it is 5 days prior to the reference date, how do you figure out how much you have? Go to the column and row on the  $^{33}\text{P}$  decay chart corresponding to 5 days postreference. There you will see the fraction 0.872. You will divide your reference activity and radioactive concentration by this number to obtain the proper amount of activity present, or  $1/0.872 = 1.15 \text{ mCi}$ . Note that the values should be greater than the stated amounts of activity and the referenced radioactive concentration. For the calculation method you are now looking for  $A_0$ . Therefore  $A_0 = A e^{0.693t/T} = 10 \exp(0.693 \times 5/25) = 11.5 \text{ mCi/ml}$ , using a half-life of 25 days for  $^{33}\text{P}$ .

### **How Long after the Reference Date Can You Use Your Material?**

Radioactively labeled compounds do not suddenly go bad after the reference date. It isn't an expiration date. It is used as a benchmark by which you can anchor your decay calculations as described above.

**Table 6.1 Shelf Lives for Commonly Used Isotopes**

|                  |             |             |
|------------------|-------------|-------------|
| <sup>32</sup> P  | Phosphorous | 1–3 weeks   |
| <sup>33</sup> P  | Phosphorous | 4–12 weeks  |
| <sup>35</sup> S  | Sulfur      | 2–6 weeks   |
| <sup>125</sup> I | Iodine      | 3–12 weeks  |
| <sup>3</sup> H   | Hydrogen    | 1–12 months |
| <sup>14</sup> C  | Carbon      | 1–2 years   |

Only you can determine how long you can use your radioisotope after the reference date. The answer depends on the isotope, the compound it's bound to, the experiment, storage, the formulation of the product, and the like. Table 6.1 lists the general ranges for the most commonly used radioisotopes, which is a guideline only. As you carry out your work, you will discover when your material starts to give poorer results.

### **Can You Compensate by Adding More Radiochemical If the Reference Date Has Long Passed?**

Sometimes it is not that simple. As an example of the complexities involved with radiolytic decomposition, suppose you had a vial of <sup>32</sup>P gamma labeled ATP that you routinely use to label the 5' end of DNA via T4 Polynucleotide kinase. If one half-life has passed since the reference date (14.28 days), you will have 50% of the stated radioactivity remaining. You might still achieve satisfactory 5' end labeling with T4 Polynucleotide kinase if you double the amount of the <sup>32</sup>P added to the reaction. Often, however, you may find that though you have compensated for the radioactive decay by adding more material, you have also introduced more of the decomposition products, which will be fragments of the original labeled compound and free radicals. You also will have added more of the solute that might be present in the stock vial. These contaminants and decomposition products can significantly interfere with the reaction mechanism and compromise your results.

## **HANDLING RADIOACTIVE SHIPMENTS**

### **What Should You Do with the Radioactive Shipment When It Arrives?**

The radiation safety officer is responsible for ensuring that radioactive materials are received in satisfactory condition, but

procedures may vary within the institution. Sometimes the RSO will check the shipping box for contamination and then discard the outer box, forwarding only the radioactive container to the researcher. At other facilities the receiving group will do a wipe test on the outer shipping container only, and if found to be uncontaminated, forward the entire package to the researcher. Upon receipt, you will want to carry out a final wipe test on the vial of radioactive material before opening, to make sure there is no gross contamination.

### *The Wipe Test*

The manner in which a wipe test is to be carried out will be described in your institution's radioactive use license, the details of which can be explained to you by your RSO. A wipe test involves dragging or rubbing a piece of absorbent paper, or cotton swab across a portion of a vial, package, or surface (the standard area being 100 cm<sup>2</sup>). You are testing for the presence of removable radioactive contamination. The paper or swab may be dry or wetted with methanol or water. Your RSO will let you know which way is preferred by the institution. After wiping the surface, the paper or swab may be placed into a liquid scintillation counter (LSC) to detect if any contamination was removed. It is usually best to count the wipes in an LSC rather than use a count-rate meter because some isotopes are not detected with a count-rate meter (e.g., tritium). Knowing the radioisotope and its decay products will help to determine the best detection method. The count-rate meter will be described more fully below.

### **A Wipe Test Detected Radioactivity on the Outside of the Vial. Does This Indicate a Problem?**

If you detect contamination on the outside of your vial, contact your RSO. She will tell you, based on experience and institutional norms, whether the amount of contamination you have found is of concern, and whether the counts detected on the LSC may be artifactual (caused by chemiluminescence), or if they are being caused by radioactive contamination.

While the ideal is to have no detectable counts on the outside of the primary container, the act of packaging, shipping, and handling can work together to make this difficult to achieve. Then there are some radioisotopes, most notably, <sup>35</sup>S and <sup>3</sup>H, that are volatile, and can leach through the crimped overseals. This is one of the reasons why radioactive materials are shipped in secondary

containers. The vial of  $^{35}\text{S}$  labeled methionine you might receive is first dispensed into a primary container, which is sealed, then placed into a secondary container. The secondary container usually has absorbent material placed in it that will absorb any liquid should there be a spill. It is always prudent to wear some thin plastic gloves when dealing with radioactive materials, especially when they first arrive and you have no indication on whether or not they are contaminated.

The NRC has set action limits to contaminated surfaces of outer packages and containers, and the RSO is required to contact the NRC when these levels are surpassed. The amount of contamination considered significant will differ, depending on whether the activity is on the primary container, secondary container, or the outer package. Based on these action levels, an institution sometimes sets its own, lower, contamination limits. Contact your RSO for more information on contamination limits.

### **Your Count-Rate Meter Detects Radiation on the Outside of a Box Containing 1 mCi of a $^{32}\text{P}$ Labeled dATP. Is It Contaminated?**

When you put a count-rate meter up to the outer package containing the  $^{32}\text{P}$  substance, you will hear clicking sounds, indicating the presence of radioactivity. To determine whether the radiation is coming from contamination on the outside of the package, or emanating from the vial of material, it is necessary to carry out a wipe test on the package. In the overwhelming majority of cases, what the instrument is detecting is called *Bremsstrahlung*.

#### *Bremsstrahlung*

*Bremsstrahlung*, or “braking radiation,” is created when a beta particle interacts with the shielding material to produce X rays. The Plexiglas™ vial that contains the radioactive material is sufficient to block essentially all beta emissions but not the X rays. Is *Bremsstrahlung* dangerous? The dose rate detected on the surface of a vial with 1 mCi of  $^{32}\text{P}$  tends to be between 1 and 5 mrem/h, while there will be no detectable dose rate three feet away. This level of dose rate is considered low for those working in occupations that use radioactivity. It is important to remember that dose rate decreases as you move away from the source. Doubling the distance from the source will quarter the radiation dose. This is known as the inverse square law, and it is applicable whenever the source can be considered a point source. You may wish to discuss dose rates in more detail with your RSO.

## **You Received 250 $\mu\text{Ci}$ of $^{32}\text{P}$ and the Box Wasn't Labeled Radioactive. Isn't This a Dangerous Mistake?**

Both the Department of Transportation (DOT) and The International Air Transport Association (IATA) have regulations concerning the labeling of packages containing limited quantities of radioactive materials (International Air Transport Association [IATA] Dangerous Goods Regulations, 6.2, and Code of Federal Regulations [CFR] 173.421, 173.422, 173.424, and 173.427). A package is defined as containing a limited quantity of an isotope if it conforms both to a certain physical amount of radioactive substance, and if the dose rate on the outside surface of the package is less than 0.5 mrem/h. For example, the isotope  $^{32}\text{P}$  has a limited quantity of 3.0 mCi if it is in liquid form. This means that if the package contains less than 3.0 mCi, and if the dose rate is less than 0.5 mrem/h on the package's surface, then it is considered to be a package of limited quantity. So the package does not require an external label which bears the marking "radioactive." The regulations do require, however, that there be such labeling somewhere inside of the package, and that the packaging itself prevent leakage of the radioactive material under "conditions likely to be encountered during routine transport (incident-free conditions). . . ." (International Air Transport Association [IATA] Dangerous Goods Regulations, 6.2).

## **DESIGNING YOUR EXPERIMENTS**

### **How Do You Determine the Molarity and Mass in the Vial of Material?**

Let's start with some definitions.

#### *Specific Activity*

The definition of specific activity is the amount of radioactivity per unit mass, and is usually reported as curies per millimole (or Becquerels per millimole), abbreviated Ci/mmol (Bq/mmol). Specific activity is a quantitative description for how many molecules in a sample are radioactively labeled.

In order to determine the ratio of labeled molecules in the total molecule population, the specific activity of the material is divided by the theoretical maximum specific activity. The theoretical maximum specific activity is defined as the greatest amount of radioactivity that can be achieved if there were 100% isotopic abundance at a single location. This number is specific to the type of radionuclide.

As a simple example, the theoretical maximum specific activity for  $^{32}\text{P}$  is 9131 Ci/mmol. If the percentage of radioactive molecules in a 3000 Ci/mmol product is desired, it simply is a matter of dividing 3000 by 9131 to find that approximately one-third of the molecules in that sample are radioactive. This will give the investigator an idea of how many radioactive molecules may get incorporated into the final product.

### *Molarity*

The molarity of a labeled compound in solution can be calculated by dividing the radioactive concentration of your radiochemical by its specific activity:

$$\frac{\text{Radioactive concentration}}{\text{specific activity}}$$

For example, a vial of  $^{32}\text{P}$ -labeled gamma ATP at a radioactive concentration of 10 mCi/ml and specific activity of 3000 Ci/mmol will have a molarity of

$$\frac{10 \text{ mCi/ml}}{3000 \text{ Ci/mmol}} = 3.33 \mu\text{M}$$

### *Moles*

Once you have the molarity of your stock solution, simply multiply that by the volume of stock you'll be adding to your reaction in order to obtain the number of moles you have

$$\text{Molarity} \times \text{volume} = \text{moles}$$

Continuing with this example, if you are adding 5  $\mu\text{l}$  of the  $^{32}\text{P}$ -ATP to your reaction, you will be adding

$$3.33 \text{ pmol}/\mu\text{l} \times 5 \mu\text{l} = 16.7 \text{ pmols}$$

to the reaction vessel. After calculating the molarity of your radioactive stock solution, you might be shocked to learn how low it is. You might even think that it's too low for the reaction to run, or perhaps your protocol states that you should start out with a higher molarity. The solution is as follows:

Make up a stock solution of the cold compound in question, at the appropriately higher molarity. To this stock or to the reaction mix itself, add the amount of radioactivity required. The number of picomoles of radiolabeled compound that you'll be adding to your reaction mix will, in most cases, be so low that

it will make no practical difference to the overall molarity of the compound. Note, however, that by adding cold compound, you will be dramatically lowering the specific activity of the radioactive label, which is in the reaction vessel. You may find that you get lower incorporation rates.

### **How Do You Quantitate the Amount of Radioactivity for Your Reaction?**

#### *DPM, CPM, and $\mu\text{Ci}$*

One curie of activity is  $3.7 \times 10^{10}$  disintegrations per second (dps) or  $2.22 \times 10^{12}$  disintegrations per minute (dpm). Thus the definition of a  $\mu\text{Ci}$  is  $2.22 \times 10^6$  dpm, regardless of the isotope involved. Disintegrations per minute (dpm) are a function of nature; counts per minute (cpm) are a function of a detection device. Cpm/dpm is a measure of the instrument's efficiency to detect an isotope's decay event. A liquid scintillation counter (LSC), because of its photomultiplier tubes, cannot be 100% efficient. The instrument will give values in cpm, which will always be lower than the true number of disintegrations occurring in the sample. This counting efficiency can vary with the isotope and even the type of solvent and scintillation fluid (if a liquid scintillation method is used) that your samples are in. The counting efficiency should be determined if quantitative results are needed in your work. The procedure is to measure the cpm detected from a sealed calibration source that contains a known number of dpm. The percent efficiency of your counter is calculated by dividing the counted cpm by the dpm as indicated on the vial, then multiplying this quotient by 100. Typical examples of counting efficiencies for some commonly used isotopes are 75 to 85% for  $^{14}\text{C}$ ,  $^{35}\text{S}$ , and  $^{33}\text{P}$ ; 35 to 55% for  $^3\text{H}$ ; 70 to 80% for  $^{125}\text{I}$  (this radioisotope, while being a gamma ray emitter, is actually more efficiently counted on an LSC); and almost 100% for  $^{32}\text{P}$ . These efficiencies are approximations only. Efficiencies can vary widely, however, depending on instrument, isotope, and sample type.

#### *The Becquerel (Bq)*

A Becquerel, or Bq, is a *Système Internationale* unit of measure for radioactivity. One Bq is one disintegration per second (dps). One dpm will be 60 Bq. One  $\mu\text{Ci}$  is defined as 37 kBq. The Bq is a defined value of radioactivity that is small, whereas the Ci is very large. In the United States, the Ci is still a common unit. Most other countries have converted to using the Bq.



## **STORING RADIOACTIVE MATERIALS**

As you gain experience with your radioactive materials, you will gain insight into two of their important but not intuitive physical properties. First, their lifetime is shorter than their unlabeled counterparts (because attached to them is a huge ball of energy waiting to blow). Second, the compound's shelf life is often dramatically less than the half-life of the isotope used to label it.

### **What Causes the Degradation of a Radiochemical?**

The mechanisms of radiolytic decomposition are fairly complex but can be divided into primary and secondary decomposition (Amersham International, 1992). Internal primary degradation is caused by the release of energy from the radioactive atom's unstable nucleus. This energy release in turn is thought to break up the bonds of the parent molecule, destroying it (for very large molecules, e.g., proteins, it is unlikely to destroy the entire molecule). The rate of primary degradation is identical to the radioactive decay rate.

Another mode of primary decomposition is external, arising when ionizing radiation emissions hit nearby molecules. The energy transferred to the molecule is often enough to break chemical bonds within the molecule producing random fragments.

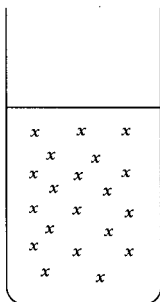
Secondary decomposition is caused by free radicals generated by the interaction of beta particles with the solvent. It is the most insidious form of decomposition. Free radicals can potentially interact with any compound within the solvent, generating innumerable contaminants and breakdown products. Some reactions generate more free radicals, leading to exponential rates of breakdown and contaminant production.

### **What Can You Do to Maximize the Lifetime and Potency of a Radiochemical?**

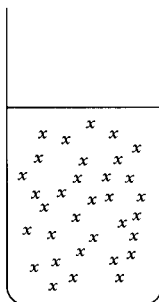
1. Do not alter the recommended storage conditions.

Colder is not always better. If the solvent containing the radioactive material is stored at a temperature that allows the solvent to freeze slowly, an event called molecular clustering will occur (Figure 6.2). The freezing solvent pushes nonsolvent molecules into pockets or clusters. This results in extremely high radioactive concentrations, which in turn will cause extremely high rates of radiolytic decomposition. Examples of solvents freezing slowly will be: water at  $-20^{\circ}\text{C}$ , or ethanol at  $-70^{\circ}\text{C}$ . If the solution is quick-frozen (in liquid nitrogen), you will avoid the effects of molecular clustering.

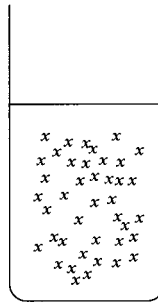
a)  
+2°C  
Unfrozen



b)  
Freeze fast  
in liquid N<sub>2</sub>



c)  
Slow freeze



**Figure 6.2** Molecular clustering effects. From *Guide to the Self-decomposition of Radiochemicals*, Amersham International, plc, 1992, Buckinghamshire, U.K. Reprinted by permission of Amersham Pharmacia Biotech.

2. Keep the radioactive concentration as low as possible to minimize primary external and secondary decomposition.
3. Minimize the number of freeze-thaws, which may increase the decomposition rate
4. Don't alter the recommended solvent.

Some solvents will cause greater rates of radiolytic decomposition. It cannot be predicted which ones will be better or worse until they have been tested. Manufacturers will have chosen the most appropriate solvent for the radioactive compound.

5. Schedule experiments to consume your store of radioisotope as quickly as possible.

### What Is the Stability of a Radiolabeled Protein or Nucleic Acid?

After labeling or incorporation of radioactivity into your molecule of interest, radiolytic decomposition occurs. As the isotope decays into the surrounding solution, there will be primary decomposition, giving rise to nicked, or broken strands in your labeled nucleic acid, as well as the less predictable secondary decomposition, which might break the chemical bonds comprising that molecule. It is best to use your labeled molecule as soon as possible, or to store in as dilute a concentration as is reasonable for your work.

In this regard, <sup>32</sup>P is the most offending of the three most commonly used radioisotopes (<sup>32</sup>P, <sup>33</sup>P, and <sup>35</sup>S). Compounds

labeled with  $^{32}\text{P}$  can have extremely high specific activities, and the energy of the beta is also extremely high. On the other hand,  $^{33}\text{P}$  and  $^{35}\text{S}$  have similar energies to each other. They have much lower emission energies and thus are less destructive to surrounding molecules. This issue is discussed in greater depth in Chapter 14, “Nucleic Acid Hybridization.”

### **Radioactive Waste: What Are Your Options and Obligations?**

It is essential to keep accurate records of the amount and type of radioactive waste that you generate. The RSO keeps track of all incoming radioactivity and all outgoing radioactive waste, so it is important to keep track of the material you use, store, and dispose of for the RSO's records. When the NRC or governing body inspects your institution, it will check its receipt and disposal records. If they are not in order, there is the possibility of suspension of your institution's license.

#### *Obligations*

Consult your RSO. Your institution has in place a detailed waste management program, and your radiation license requires that you follow your institution's waste handling procedure without variance. Minimally you must separate the waste of different nuclides, and you will probably be required to separate liquid and solid wastes and to minimize the creation of mixed waste, which is discussed further below.

#### *Options*

Generate no more radioactive waste than is absolutely necessary. Most countries have few sites that accept radioactive waste, so the costs per pound are outrageously expensive, forcing more institutions to store waste locally. Although there have been major advances in radioactive waste processing, these new technologies may be years away from being commonly available to any but the largest producers of radioactive waste.

Radioactive waste can be treated as nonradioactive after 10 half-lives. This is convenient for isotopes with short half-lives, such as  $^{32}\text{P}$  and  $^{33}\text{P}$  (10 half-lives is 250 days for  $^{33}\text{P}$ , 143 days for  $^{32}\text{P}$ ), but the very long half-lives of  $^{14}\text{C}$  (5730 years) and  $^3\text{H}$  (12.41 years) more urgently illustrate the need for waste reduction. Your institution will have a policy on which radioisotopes will be disposed of by “decay in storage” or dumping into the sanitary sewer.

Limit the production of mixed waste, which is defined as a combination of two or more hazardous compounds, such as scintilla-

tion fluid and radioactivity. This waste is especially expensive to process and it will be worth your time to investigate if this type of waste can be avoided or minimized.

## **HANDLING RADIOACTIVITY: ACHIEVING MINIMUM DOSE**

### **How Is Radioactive Exposure Quantified and What Are the Allowable Doses?**

Radiation exposure is defined in REM, or “radiation equivalent man,” and mrem, or millirem. In the United States, the maximum annual allowable dose is 5000mrem to the internal organs, and 50,000mrem to the extremities for those individuals working with radioactivity. (Note: Most other countries use a similar level, but the units are the international units of Sieverts, 5000mrem = 50mSv.) For comparison, the average person who doesn’t work with radioactivity receives between 300 and 500mrem per year. They receive this exposure from sources such as  $^{40}\text{K}$  (potassium-40) and other naturally occurring radioactive isotopes found in foods, soil and rock, radon gas, cosmic rays, medical and dental X rays, and so forth.

### **Monitoring Technology: What’s the Difference between a Count-Rate Counter and a Dose-Rate Meter?**

#### *Count-Rate Meter*

A count-rate meter, generally configured with a Geiger-Müller detector, is used to detect small amounts of surface contamination. It is a common laboratory instrument. The unit is small and hand-held with an attached probe. When the probe face is directed toward an appropriate radiation field (most beta or gamma emitters), the count-rate meter produces the familiar clicking sound made so famous in science fiction movies of the 1950s. On the body of the meter is either an analog needle-type gauge or a digital readout, which will indicate the counts per second (cps) or counts per minute (cpm) of the field based on where the probe is located. In general, the efficiency of the count-rate meter versus a liquid scintillation counter, for example, is quite low. It has been designed to provide a quick, qualitative means of determining the presence of minute quantities of radioactivity (most instruments will detect between 50 and 5000 cps).

In the presence of a significant radiation field, the count-rate meter will be overloaded and cease to “click” or give a reading on the needle gauge. You can misinterpret the lack of sound

as meaning that no dose field is present, when in fact what you need is another type of instrument to detect dose rates. The count-rate meter is best used to detect nanocurie or less quantities of contamination on gloves, benchtop, and other equipment.

### *Dose-Rate Meters*

The dose-rate instrument should be used to detect larger quantities of ionizing radiation. It measures radiation fields in units of mrem/h. The dose rate meter also has a probe, generally an ionization chamber, and registers values on an analog needle gauge, or digital reading. A dose-rate meter does not aurally indicate the presence of radioactivity with clicks, however. It converts detected nuclear events into units that can be related to how much radioactive dose is present. This conversion is dependent on type and energy of emission, as well as on the distance from the radiation source. A count-rate meter detects an event, while a dose-rate meter converts that event into a meaningful energy reading. It is not a simple matter to convert cpm into a dose rate of mrem/h in our heads or by use of a chart because of the number of variables involved. Where a count-rate meter will go off scale, or become overloaded in a modest radiation field of 10 mrem/h, a dose-rate meter can measure much greater readings, depending on the particular instrument. Dose-rate meters are generally more expensive and not normally present in a lab, but your RSO will have them on hand when one is needed.

An illustration of the difference between dose rate and counts per second (or per minute) is seen in the following example. If you place a 1 mCi vial of  $^{32}\text{P}$ -labeled dCTP right next to the probe face of a count-rate meter, there would suddenly be an “alarm-ing” clicking sound. If you were to then open the vial, face the probe vertically down toward the open solution of  $^{32}\text{P}$ , the meter would almost immediately become overloaded and stop giving off any sound, and fail to register a value on the needle gauge (The author does not recommend that you actually do this as it will needlessly increase both your exposure and the editor’s legal liability.)

If you were to place the same sealed vial directly next to a dose-rate meter, you will detect an exposure rate of 2 to 5 mrem/h, which is typically considered to be a low or modest exposure dose field. If the dose-rate meter’s probe is one inch directly above the open vial, you will read in excess of 1.0 rem/h, or 1000 mrem/h, a dramatic increase in dose. This is a significantly higher dose

rate, yet the count-rate meter would not provide you with any warning.

To relate this scenario into the amount of exposure a dose film badge or thermoluminescent dosimeter (TLD) used for personnel monitoring might detect, suppose that your hand with a finger badge were placed directly over the open vial for one minute. Your finger might receive close to 17 mrem, which can quickly add up if it is part of your routine. On the other hand, if you held the closed vial in your hand for one hour, the finger dosimeter would register only 5 mrem, or 0.01% of the annual allowable dose.

### **What Are the Elements of a Good Overall Monitoring Strategy?**

#### *Identify the Hot Spots*

Consider inviting your RSO to inspect the organization of your radioactive work area and to monitor your laboratory with a dose-rate meter to identify locations of significant exposure. This step is especially relevant when working with strong emitters such as  $^{32}\text{P}$  and  $^{125}\text{I}$ .

#### *Short Term, or Contamination Monitoring*

At the start of each workday, use a count-rate meter to check any work surface you plan to encounter, such as the benchtop and the lip of the hood. Next apply a count-rate meter to monitor the entire front part of your body and legs; pay special attention to your gloves and lab coat, especially the sleeves.

In all cases of contamination of yourself or if a serious spill occurs, your institution will have a very clear procedure on what steps to take to resolve it. You must know this procedure before working with radioactivity in your lab.

#### *Long Term, or Dose Monitoring*

Whole body dosimeters, often referred to as “badges” should be worn on the chest or abdomen to estimate exposure to critical organs. Ring badges worn on fingers are recommended to monitor extremity exposure. In some cases, and with particular radioisotopes in use, the radiation safety officer may require more specific monitoring techniques in order to test for the presence of radioactive contamination. A common example is the requirement of urine samples from those investigators working with tritium, and thyroid monitoring for those working with radioactive iodine.

## **What Can You Do to Achieve Minimum Radioactive Dose?**

### *Attitude*

Consider the benefits of an attitude whereby everyone working with radioactivity continuously ponders if they are working in the safest, most efficient manner. Is a particular radioactive experiment necessary? Can the amount of radioactivity in an experiment be reduced? Is there a faster, safer way to carry out the work? Questions like these will reduce cost and radioactive exposure. An institution's RSO is also required to implement a continuing education program regarding the principles of keeping personnel exposure dose low.

If you find yourself becoming stressed while handling radioactivity, or if that "incessant clicking sound" of the count-rate meter is causing a heightened sense of alarm, you can always step away from the bench to put things into perspective. Estimate how much dose you are receiving from your activities and relate those back to your annual allowable dose.

### *Time*

Work quickly and neatly. In the example above, a finger lingering for 1 minute over an open 1 mCi vial of  $^{32}\text{P}$  will receive 17 mrem, whereas a 10 second exposure receives a sixfold lower dose.

Practicing the manipulations of your experiments with non-radioactive materials will identify problem areas and ultimately enable you to work faster and safer. Working with radioactivity while feeling panicked or rushed will slow you down or cause an accident. If you can't smoothly do the motion in 10 seconds, take 20. You'll improve through time and all along will be well aware of your estimated dose. You'll automatically be striving to lower your dose.

### *Distance*

Dosage decreases with distance. Why? A radiation source is like a light bulb. As the rays radiate outward in a sphere, they cover a wider area but become less potent at any single point. Use the inverse square law to your advantage. Can you pipette with a longer pipettor? Can you place the reaction vial even a few inches farther from you and others in the lab? Can you place a film cassette containing a radioactive membrane farther away from your work area? Small steps such as these can go a long way in reducing dose to you and your colleagues.

## *Shielding*

A good shielding strategy will effectively reduce dose rate without preventing you from working smoothly and safely. It will not force you to get closer or stay longer in high radiation areas. If the use of lead-lined gloves makes you feel like you're working in a vat of honey and increase the likelihood of a spill, you might want to consider alternative shielding.

### Shielding for Beta Emitters

Acrylic plastic (Plexiglas<sup>TM</sup>) is used for the pure beta emitters, like  $^{32}\text{P}$ ,  $^{33}\text{P}$ , and  $^{35}\text{S}$ . A half inch thick piece of acrylic will stop essentially 100% of all betas, even for strong emitters, such as  $^{32}\text{P}$ .

### Shielding for Gamma Emitters

Lead will attenuate rather than completely obstruct gamma or X radiation. You may see in some literature that for a particular gamma-emitting isotope, a certain thickness of lead is required to "reduce the dose rate by a factor of 10." This means that if a source is giving off a field of 100 mrem/h without shielding, the dose rate with that particular thickness of lead will be brought down to 10 mrem/h. For example,  $^{125}\text{I}$  needs to have 0.25 mm of lead shielding in order to reduce the dose rate by a factor of 10. Each successive layer of 0.25 mm will continue to decrease the dose rate by a factor of 10.

Lead is best used as shielding for an isotope giving off both gamma radiation and beta particles, rather than a combination of acrylic and lead.

### Volatile Nuclides

The three isotopes you are likely to encounter with volatile properties are  $^3\text{H}$ ,  $^{35}\text{S}$ , and  $^{125}\text{I}$ . Their chemical properties and the incredibly complex reactions involved with radiolytic decay cause these two isotopes to form gaseous by-products. If you work with any of these isotopes, your RSO and institution may have approved fume hoods for their use.

### Isotopes That Do Not Require Shielding

Tritium, being a very weak beta emitter, travels only a few microns in air. Acrylic shielding would be of no use. What you do not want to do is to ingest tritium. Tritium in an aqueous form is 25,000 times more radiotoxic than tritium in a gaseous form.



## **How Can You Organize Your Work Area to Minimize Your Exposure to Radioactivity?**

If feasible, select bench space at the corner of the room, rather than in a central location, to reduce unnecessary traffic. Clearly delineate this work area as radioactive. Although it is not always possible due to space restrictions, it is recommended that if your lab is working with different radioisotopes that there be separate work areas for each radioisotope. Check with your RSO about any additional requirements listed on the institution's license.

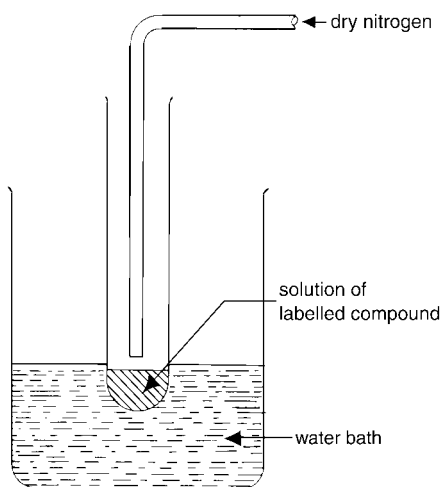
Of main importance will be arranging your work space. Begin with absorbent material, perhaps a double thick section, taped onto the bench. A waste container that shields against the radioactivity should be placed in a location that makes it easy, quick, and safe to dispose of pipette tips, hot gloves, and the like. A box made of acrylic with a lid is sufficient for  $^{32}\text{P}$ ,  $^{33}\text{P}$ , and  $^{35}\text{S}$ , while for  $^{125}\text{I}$ , lead-impregnated acrylic will help attenuate the gamma rays. Each radioisotope may need its own separate container for waste, depending on your institution's disposal protocols.

If you are using  $^{32}\text{P}$ , acrylic shielding between you and the source is strongly recommended. There are many commercially available shields that will meet your needs. Once you establish your radioactive area, do a couple of practice runs to make sure that your work area is properly organized. Bring the RSO in so that she/he can approve your radioactive area and perhaps make further suggestions.

You'll want to examine closely any areas or actions that have the potential for high doses. An open vial of  $^{32}\text{P}$ , an Eppendorf tube with  $50\mu\text{l}$  of  $^{32}\text{P}$ , and a tray containing your blot with hybridization solution mixed with radioactive probe will all be obvious areas where you'll need to pay close attention. The open vial may simply need an acrylic pipette guard on your pipettor in order to bring the dose down 10,000 fold. The Eppendorf incubation tube can be kept in an acrylic box, or behind acrylic shielding while the labeling reaction is going on. You may devise a way of not picking the reaction tube up with your fingers while you remove the reaction mix with a pipettor. The blotting container may present a potential spill. Finding a safe, out-of-the-way place, preferably in a fume hood and behind some acrylic shielding will go a long way toward reducing dose.

## **How Can You Concentrate a Radioactive Solution?**

Three convenient approaches are lyophilization, a spinning vacuum chamber, and drying with a gentle stream of nitrogen gas.



**Figure 6.3** Removal of solvent from a non-volatile radiochemical using dry nitrogen. From *Guide to Working Safely with Radio-labelled Compounds*, Amersham International, plc, 1974, Buckinghamshire, U.K. Reprinted by permission of Amersham Pharmacia Biotech.

There is significant risk of contamination when using a lyophilizer or spinning vacuum chamber, so most facilities dedicate specific equipment for radioactive work. Blowing a very gentle stream of nitrogen gas over the solution works efficiently, but practice is required to avoid blowing the radioactive solution out of its container.

The nitrogen stream method is straightforward (Figure 6.3). Attach a small glass pipette/dropper tip to tubing that is attached to the gas regulator of a tank of dry nitrogen gas, being careful not to break the top of the pipette into your hand. Turn on the gas flow, keeping the gas flow as gentle as possible. This procedure requires very little nitrogen flow. Before impinging upon the surface of the radioactive material, test the gas flow on a vial containing a like amount of water. Adjust the flow so that there is no splashing of the liquid but only a noticeable indentation of the liquid's surface. Once you are satisfied that it is safe, gently direct the stream of gas onto the surface of the radioactive liquid, ensuring no splashing. Do all of this in a hood and in a location that is safe and will be able to contain accidental spills.

Continue blowing off the solution until dryness. Overdrying can sometimes be of concern, so it is best not to leave the area and come back to it after an extended period. It is also best to bring the solution to complete dryness so that when you bring it up into a known amount of solution, you will have an accurate idea of the concentration.

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## Appendix A. Physical Properties of Common Radionuclides

| Radionuclide         | Halflife   | Beta Energy, max(MeV)         | Specific Activity, max                                    |
|----------------------|------------|-------------------------------|-----------------------------------------------------------|
| Tritium (hydrogen-3) | 12.4 years | 0.0186                        | 28.8 Ci/matom <sup>a</sup><br>1.06 TBq/matom <sup>a</sup> |
| Carbon-14            | 5730 years | 0.156                         | 62.4 mCi/matom<br>2.31 GBq/matom                          |
| Sulfur-35            | 87.4 days  | 0.167                         | 1.49 kCi/matom<br>55.3 TBq/matom                          |
| Phosphorus-32        | 14.3 days  | 1.709                         | 9.13 kCi/matom<br>338 TBq/matom                           |
| Phosphorous-33       | 25.3 days  | 0.249                         | 5140 Ci/matom                                             |
| Iodine-125           | 59.6 days  | Electron capture <sup>b</sup> | 2.18 Ci/matom<br>80.5 TBq/matom <sup>a</sup>              |

Source: Data reproduced from *Guide to Working Safely with Radiolabelled Compounds* (Amersham International, 1974).

<sup>a</sup> A milliatom is the atomic weight of the element in milligrams.

<sup>b</sup> Electron capture is a radioactive transformation in which the nucleus absorbs an electron from an inner orbital. The remaining orbital electrons re-arrange to fill the empty electron shell and in so doing energy is released as electromagnetic radiation at X-ray wavelengths and/or electrons.